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(54) Title: MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE

(54) Titre: MANCHON MULTICOUCHE POUR DISPOSITIF INTRAVASCULAIRE EXPANSIBLE

(57) Abstract

The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example. More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve (1, 2) for encompassing an expandable device (3), such as a stent, to be introduced into a body canal, such as a blood vessel for example. Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.

(57) Abrégé

La présente invention concerne un manchon multicouche destiné à envelopper un dispositif expansible devant être introduit dans un canal du corps, tel qu'un vaisseau sanguin par exemple. Plus particulièrement, la présente invention concerne un manchon (1, 2) multicouche de libération d'agents thérapeutiques destiné à envelopper un dispositif (3) expansible tel qu'une prothèse endovasculaire devant être introduit dans un canal du corps, tel qu'un vaisseau sanguin par exemple. Ainsi, la présente invention peut être d'abord appliquée au traitement de troubles dans des canaux du corps comprenant une paroi de canal et une lumière par laquelle s'écoule un fluide corporel. L'oesophage, l'urètre, et les vaisseaux sanguins coronaires et périphériques constituent des exemples de ces canaux du corps.

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MULTI-LAYERED SLEEVE FOR INTRAVASCULAR EXPANDABLE DEVICE

The present invention relates to a multi-layered sleeve for encompassing an expandable device to be introduced into a body canal, such as a blood vessel for example and to a method of manufacturing such a sleeve.

More particularly, the present invention relates to a therapeutic agent-releasing multi-layered sleeve for encompassing an expandable device, such as a stent, to be introduced into a body canal, such as a blood vessel for example.

Hence, the present invention is primarily applicable to the treatment of disorders of body canals comprising a canal wall and a lumen through which a body fluid flows. Examples of such body canals are the oesophagus, the urethra, and the coronary and peripheral blood vessels.

Disorders of body canals, such as coronary arteries for example, are generally caused or provoked by the presence, on the inner walls of the canal, of deposits which cause strictures or stenoses in said canal.

The treatment of such disorders generally calls for the use of an inflatable device, such as a dilatation catheter for example, for restoring the normal section of flow of the canal at the level of the stenosis. In a certain number of cases, the result is further optimised through implantation of an expandable device in order to provide support to the vessel wall.

Such expandable devices are well-known in the field of medicine for implantation in blood vessels, biliary ducts, or indeed other similar organs of the living body. They generally fall into two categories : those known as self-expandable prostheses, and those which require a forced expansion with the aid of a balloon for example ; both types are commonly known as stents in the cardiovascular field. Such expandable devices are used to maintain, open, or dilate tubular structures or to support tubular structures

(for example by the method disclosed in EP-A-0 797 963, which involves dipping the stent in a solution of a polymer in a solvent, followed then by the evaporation of the solvent) or is covalently bound to the metal. The polymer is bonded to or contains an anticoagulant compound. Most coated stents currently under development use heparin as the active ingredient. One of the more effective polymer coated stent is Biogold (van der Giessen *et al.*, Circulation, 1990, 82 :III-542). Biogold and other coated stents have not however completely prevented arterial thrombosis. This is probably due to the cracking of the polymer as the stent is expanded during deployment, saturation of the anticoagulant binding sites on the stent, and/or the inadequacy of heparin as an anticoagulant in the prevention of arterial thrombosis and/or too small quantities of therapeutic agent in comparison with the total surface of arteries wall covered by the stent. It is because of these inadequacies associated with polymer coatings directly applied to stent wires that there remains a great need to effectively prevent vascular response at the site of the stent.

US 5,383,928 (EMORY UNIVERSITY, United States of America) entitled "Stent sheath for local therapeutic agent delivery" discloses a stent sheath for local therapeutic agent delivery. More specifically, the patent discloses a sheath for encompassing at least a portion of a stent to locally deliver a drug to an arterial wall or lumen into which the stent has been inserted, comprising a polymer and a drug incorporated within the polymer, the polymer sheath encompassing at least a portion of the stent and having a thickness to allow controlled release of the drug.

The major disadvantage of the sheath according to this prior art document resides in the fact that in order to change the therapeutic agent or adapt the therapeutic agent release rate incorporated therein, it is necessary to change the entire sheath itself (thickness, nature of polymer(s) etc.). Consequently, the whole mechanical properties of the entire sheath would also be changed.

the sleeve, the sleeve would have to be of a thickness pre-determinable according to the amount of therapeutic agent(s) it is desired to be released i.e. the thicker the sleeve, the more therapeutic agent(s) it may contain and release, and, finally,

(h) able to optionally encompass an expandable device, a stent for example, it being possible for said expandable device to be either embedded within said sleeve, or disposed radially and internally with respect to said sleeve, according to the needs of the patient.

The inventors of the present invention have carefully addressed the above-mentioned requirements and have been able to provide a solution to the present technical problem in the form of a sleeve which is comprised not of just a mixture of polymers, but a system of polymer layers.

More importantly, the sleeve in accordance with the present invention is comprised of a system of polymer layers which are actually able to adhere together without affecting the elasticity and mechanical properties of the sleeve resulting therefrom in any way whatsoever, and which thus provides a solution to the present technical problem in the form of a sleeve having highly advantageous properties over those of the prior art in a totally unexpected way.

Thus, according to a first aspect, the present invention provides a sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic layer being such that predetermined mechanical properties of said sleeve be provided.

According to a second principal aspect, the present invention provides a sleeve for encompassing an expandable device for introduction

in nature and which exhibits the characteristic macromolecular structure of a gel. A gel is best described as a continuous three-dimensional network that is held together by chemical or physical bonds. Sufficient interstitial space exists within the network, and water molecules can become trapped and immobilised, filling the available free volume. Gels can be divided into two major categories based on the types of bonds that comprise them. These include chemical gels and physical gels.

Advantageously, the above-mentioned sleeve is characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a material selected from the group consisting of polyurethane, silicone, and latex. The material needs to have a good elasticity that is an elongation of at least 500% (PU tensile strength 7,500 psi elongation 500%, latex tensile strength 85 kg/cm^2 elongation 700%, silicone tensile strength 1310, elongation 1000%) and a good flexure resistance in vivo (no oxidation of the material even if the sleeve is stretched).

The nature of the hydrogel and the appropriate thickness of a layer or film containing same shall be easily determined by the person skilled in the art in taking into consideration the specific nature of the therapeutic agent(s) to be released therefrom.

Also advantageously, the above-mentioned sleeve is characterised in that said hydrogel outer and inner layers independently comprise at least one hydrophilic polymer selected from the group consisting of polyhydroxyethyl methacrylate, polyvinyl alcohol, polyacrylamide, poly(N-vinylpyrolidone), polyethylene oxide, hydrolysed polyacrylonitrile, polyacrylic acid, polymethacrylic acid, polyethylene amine, alginic acid, pectinic acid, carboxy methyl cellulose, and hyaluronic acid.

Such hydrophilic polymers are particularly preferred within the context of the present invention because they possess a capacity to act as a vehicle for the therapeutic agent(s) useful for treating a body canal, and, more importantly, because they are able, once mixed with other polymers

anti-platelet receptor antibody, aspirin, a prostaglandin inhibitor, a platelet inhibitor, a tick anti-platelet peptide, or a combination thereof ; a promoter of vascular cell growth, such as a growth factor stimulator, a growth factor receptor antagonist, a transcriptional activator, a translational promoter, or a combination thereof ; an inhibitor of vascular cell growth, such as a growth factor inhibitor, a growth factor receptor antagonist, a transcriptional repressor, a translational repressor, an antisense DNA, an antisense RNA, a replication inhibitor, an inhibitory antibody, an antibody directed against growth factors, a bifunctional molecule consisting of a growth factor and a cytotoxin, and a bifunctional molecule consisting of an antibody and a cytotoxin, or a combination thereof ; a cholesterol-lowering agent, a vasodilating agent, an agent which interferes with endogenous vasoactive mechanisms, or a combination thereof ; or a smooth muscle inhibitor, such as an agent which modulates intracellular calcium binding proteins, a receptor blocker for contractile agonists, an inhibitor of the sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor agonist, an antimitotic agent, an immunosuppresive agent, a protein kinase inhibitor, or a combination thereof ; or a combination thereof.

According to a third principal aspect, the present invention provides a system for introduction into a body canal, characterised in that it comprises an expandable device and a multi-layered sleeve in accordance with the present invention.

According to an advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is embedded within said biocompatible, non-biodegradable elastic polymer layer.

According to a further advantageous variant, the present invention provides a system which is characterised in that said expandable device for introduction into a body canal is disposed radially and internally with

internally with respect to said multi-layered sleeve, represented in a body canal;

Figure 1A is a view in cross section of Figure 1;

Figure 2 is a longitudinal schematic view, similar to Figure 1, illustrating a second preferred embodiment of the sleeve according to the invention, in which the stent is embedded within the biocompatible, nonbiodegradable elastic polymer inner layer of said sleeve;

Figure 2A is a view in cross section of Figure 2.

In all Figures 1A, 1B, 2A, and 2B,

1 represents the at least one, optionally therapeutic agent(s)-containing, hydrogel outer layer of the multi-layered sleeve in accordance with the present invention,

2 represents the at least one biocompatible, non-biodegradable elastic polymer layer of the multi-layered sleeve in accordance with the present invention,

3 represents the expandable device for introduction into a body canal; and

4 represents at least one, optionally therapeutic agent(s)-containing, hydrogel inner layer of the multi-layered sleeve in accordance with the present invention.

The multi-layered sleeve is advantageously manufactured by a dipping process in which a mandrel is successively dipped in a solution in which there are different components, polymers and solvents. This successive dipping process builds up the different layers of the sleeve, as detailed above, and also ensures that, should an expandable device such as a stent be incorporated, such a device may, if required, be fully embedded in the finished sleeve. Layers which are required to be thicker than one dipping can provide are made by multiple dippings of the same component until the required thickness has been built up. Each dipping step consists in vertically immersing the mandrel in the different solutions

retrieved from the mandrel and reversed (i.e. turned inside out, or transposed). The membrane is inserted onto a translumenal prosthesis (stent).

The translumenal prosthesis is placed onto a 3.5 PTCA catheter and is inflated at the 3.5 mm diameter.

The translumenal prostheses are then tested for anti-clotting properties in comparison with the translumenal prosthesis without the hydrogel inner layer.

The inner surfaces were then extracted in human plasma at 37°C for 7, 10, 21 or 28 days and then tested for anti-clotting properties. The results obtained are shown in the Table.

TABLE

SAMPLE	CLOTTING TIME (minutes)
Uncoated sample	12
coated sample without extraction of plasma	did not clot
coated sample with 7 days extraction in plasma	did not clot
coated sample with 10 days extraction in plasma	did not clot
coated sample with 21 days extraction in plasma	24
coated sample with 28 days extraction in plasma	20

EXAMPLE 2:

PREPARATION OF A SLEEVE WITH THE SAME HYDROGEL INNER AND OUTER LAYERS

A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

The translumenal prothesis (stent) is put onto the mandrel and the sleeve and is crimped on it.

The mandrel is dipped again in the polyurethane solution. The mandrel is cured again at 75°C for 20 minutes.

The mandrel is then dipped in the hydrophilic solution (7.5% PVP solution) and is then cured at 75°C for 30 minutes.

The translumenal prothesis is placed onto 2-4 PTCA catheter and is inflated at the 2-4 mm diameter.

EXAMPLE 4:

PREPARATION OF A SLEEVE WITH HYDROGEL OUTER LAYER

A 7% solution of polyurethane in N,N-dimethylacetamide is prepared.

A hydrophilic solution is prepared as follows:

polyvinylpyrrolidone 1 g

nitrocellulose 0.12 g

ethanol 9 ml

dimethylformamide 3.0 ml

ethyl acetate 0.4 ml

Two mandrels (A and B) of 1.25 mm in diameter are dipped in the polyurethane solution. The dipped mandrels are cured at 75°C in an oven for 20 minutes. The mandrels are dipped again in the polyurethane solution, and cured again at 75°C for 20 minutes. The mandrel A is then dipped in the hydrophilic solution and cured for 30 minutes at 75°C.

The sleeve is retrieved from the mandrels. A tensile test is done on the two wet sleeves at 37°C. The two curves are identical up to 1000% elongation.

a chemotherapeutic agent is released directly into the urethra via the translumenal prosthesis implanted as an endoluminal prosthesis. Since a sleeve according to the present invention is used for delivering the therapeutic agent(s) and not the translumenal prosthesis itself the quantities of therapeutic agent are bigger than can be achieved with a coated translumenal prosthesis.

CLAIMS

1. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which one synthetic, hydrogel inner layer and/or one synthetic hydrogel outer layer is bound, said hydrogel inner layer being optionally different from said hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic. layer being such that pre-determined mechanical properties of said sleeve be provided.

2. A sleeve for encompassing an expandable device for introduction into a body canal, characterised in that said sleeve is multi-layered and comprises at least one biocompatible, non-biodegradable elastic polymer layer onto which at least one synthetic therapeutic agent(s)-containing hydrogel inner layer and/or at least one synthetic therapeutic agent(s)-containing hydrogel outer layer is bound, said therapeutic agent(s)-containing hydrogel inner layer being optionally different from said therapeutic agent(s)-containing hydrogel outer layer, the nature and thickness of said biocompatible, non-biodegradable elastic polymer layer being such that predetermined mechanical properties of said sleeve be provided, and the nature and thickness of said therapeutic agent(s)-containing hydrogel inner and outer layers being such that a pre-determined rate of release of said therapeutic agent(s) be controlled.

3. The sleeve according to claim 1 or 2, characterised in that said biocompatible, non-biodegradable elastic polymer layer comprises a synthetic material selected from the group consisting of polyurethane, silicone, and latex.

4. The sleeve according to any one of claims 1 to 3, characterised in that said inner and outer synthetic hydrogel layers independently comprise at least one hydrophilic polymer selected from the group consisting of

growth factors, a bifunctional molecule consisting of a growth factor and a cytotoxin, and a bifunctional molecule consisting of an antibody and a cytotoxin, or a combination thereof ; a cholesterol-lowering agent, a vasodilating agent, an agent which interferes with endogenous vasoactive mechanisms, or a combination thereof; or a smooth muscle inhibitor, such as an agent which modulates intracellular calcium binding proteins, a receptor blocker for contractile agonists, an inhibitor of the sodium/hydrogen antiporter, a protease inhibitor, a nitrovasodilator, a phosphodiesterase inhibitor, a phenothiazine, a growth factor receptor agonist, an antimitotic agent, an immunosuppresive agent, a protein kinase inhibitor, or a combination thereof; or a combination thereof.

10. A system for introduction into a body canal, characterised in that it comprises an expandable device and a multi-layered sleeve according to any one of claims 1 to 9.

11. The system according to claim 10, characterised in that said expandable device for introduction into a body canal is embedded within said biocompatible, non-biodegradable elastic polymer layer.

12. The system according to claim 10, characterised in that said expandable device for introduction into a body canal is disposed radially and internally with respect to said inner hydrogel layer.

13. The system according to any one of claims 10 to 12, characterised in that said expandable device for introduction into a body canal is a stent.

14. The system according to any one of claims 10 to 13, characterised in that it is intended to be introduced into a body canal comprising a canal wall and a lumen through which a body fluid flows and in that said sleeve comprises a therapeutic agent(s)-containing hydrogel inner layer which contains one or more therapeutic agents capable of treating a disorder of said body fluid, and a therapeutic agent(s)-containing hydrogel outer layer which contains one or more therapeutic agents capable of treating a disorder of said body canal wall.

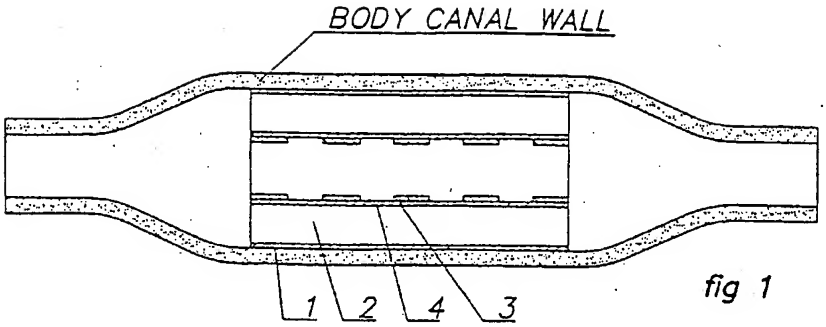

fig 1

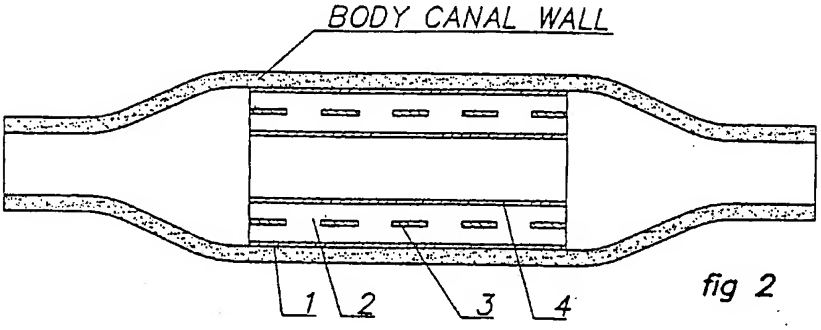

fig 2

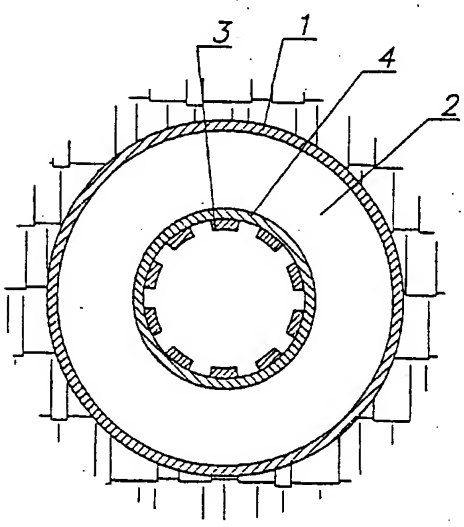

fig 1A

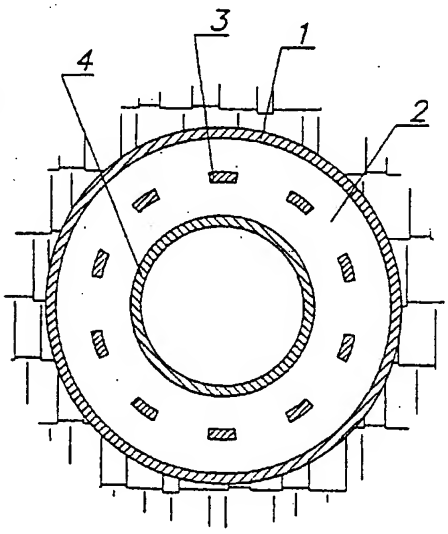

fig 2A

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9529647 A	09-11-1995	EP 0746375 A	11-12-1996
		EP 0754017 A	22-01-1997
		JP 9503945 T	22-04-1997
		JP 10503663 T	07-04-1998
		WO 9511055 A	27-04-1995
		US 5693085 A	02-12-1997
US 5383928 A	24-01-1995	NONE	
WO 9510989 A	27-04-1995	US 5735897 A	07-04-1998
WO 9623602 A	08-08-1996	CA 2211651 A	08-08-1996
		EP 0806992 A	19-11-1997
		JP 10502856 T	17-03-1998
WO 9829148 A	09-07-1998	EP 0956056 A	17-11-1999
WO 9306792 A	15-04-1993	US 5968092 A	19-10-1999
		US 5464450 A	07-11-1995
		US 5551954 A	03-09-1996
		US 5500013 A	19-03-1996
		US 5769883 A	23-06-1998
WO 9838947 A	11-09-1998	NONE	
US 5443458 A	22-08-1995	NONE	
US 5304121 A	19-04-1994	CA 2098984 A	29-06-1992
		DE 69131486 D	02-09-1999
		EP 0565604 A	20-10-1993
		EP 0920843 A	09-06-1999
		JP 6503984 T	12-05-1994
		WO 9211896 A	23-07-1992
		US 5674192 A	07-10-1997
		US 5954706 A	21-09-1999
		US 5843089 A	01-12-1998
		WO 9211895 A	23-07-1992
EP 0604022 A	29-06-1994	CA 2111455 A	23-06-1994
		JP 6218063 A	09-08-1994
WO 9944665 A	10-09-1999	NONE	